REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1, 3-4, 11-28, 41, 62 and 63, and new Claims 64-68, the only claims pending and under examination.

FORMAL MATTERS

Claims 1, 3, 4, 11-28, 41, 62 and 63 have been examined and rejected.

Claims 29-40, and 42-61 have been previously withdrawn.

Claims 2 and 5-10, 56, and 58-61 have been canceled.

Claim 1 has been amended. Support for this amendment can be found, for example, in the specification on p. 48, lines 24-29. New Claims 64-68 have been added. Support for new claim 64 can be found in the specification, for example, on p. 49, lines 22-30. Support for new claim 65 can be found in the specification, for example, on p. 48, line 30 to p. 49, line 21, and p. 50, lines 23-31. Support for new claims 66-68 can be found in the specification, for example, on p. 50, lines 8-31. Accordingly, no new matter has been added. As no new matter has been added by the above amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejection - 35 U.S.C. § 112

Claims 1, 3, 4, 11-28, 41, 62 and 63 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, paragraph 1 "Written Description" Requirement (Federal Register 66, No. 4, January 5, 2001; hereinafter the "Written Description Guidelines") provides instructions for

examining patent applications for compliance with the written description requirement of 35 U.S.C.§112, first paragraph.

The Written Description Guidelines state:

(1) There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed;

(2) The Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims;

(3) Consequently, rejection of an original claim for lack of written description should be rare;

(4) An Examiner should review the entire application to understand how Applicant provides support for the claimed invention; and

(5) Such a review is conducted from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art.

In making the rejection, the Examiner has stated that the specification does not provide support for administering a beta-blocker to treat a subject for at least one of the conditions in Claim 1, wherein modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. The Examiner has further alleged that the specification does not provide adequate description and there are no specific examples to provide support to the claims (Office Action, p. 3)

The Applicants respectfully disagree. The specification does provide adequate description for methods of administering beta-blockers to treat a subject, for example, on p. 14, line 14 to p. 25, line 4. Additionally, disclosure of conditions that may be treated using the subject methods can be found, for example, on p. 56, lines 3-11, and p. 57, lines 10 to p. 59, line 11. There are specific examples disclosed in the specification, for example, as in the treatment of sudden infant death syndrome (SIDS), or conditions associated with aging. In the example of SIDS, (as disclosed on p. 59, lines 19-25, and p. 60, line 20 to p. 61, line 12) the inventors have discovered that a maladaptive shift to sympathetic bias may be a key determinant of SIDS, and cite

multiple references in support of this assertion. In the example of aging-associated conditions (as disclosed on p. 65, line 20 to p. 67, line 12), the inventors have determined that many conditions of aging are manifestations of sympathetic bias unmasked by withdrawal of parasympathetic function. Additional citations in support of this assertion can be found on p. 66, lines 13-27.

Furthermore, the specification also clearly describes the method of treatment wherein the activities of the parasympathetic and sympathetic functions are substantially equal, as for example, on p. 10, lines 11-15. The specification also clearly describes the method of determining that the parasympathetic and sympathetic functions are substantially equal, for example on p. 48, lines 24-29.

Therefore, the Applicants maintain that there is adequate written description in the specification in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. The Examiner has not established with sufficient evidence why a person skilled in the art would not recognize that the written description of the invention provides support for the claims, and therefore, the Applicants respectfully request that the rejection of Claims 1, 3, 4, 11-28, 41, 62 and 63 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1, 3, 4, 11-28, 41, 62 and 63 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled by the specification.

The Examiner alleges that the specification does not provide sufficient guidance for the current claims. The Examiner alleges that the prior art, while being enabling for a method of treating a subject for a condition caused by an autonomic nervous system abnormality with a beta-blocker for conditions like asthma, hypertension, glaucoma, migraine, and anxiety disorders, does not reasonably provide enablement for treating all the disorders listed in Claim 1, with the non-beta blocking agents listed in Claim 24 (Office Action, p. 4).

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the

disclosure in the patent coupled with information known in the art without undue experimentation."[1]

Under *In re Wands*, a determination of enablement requires consideration of eight factors, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.[2] Accordingly, under *In re Wands*, a determination of enablement is based on the combination of the factors, taken as a whole, not based solely on a single factor.

The Applicants maintain that the present application does provide sufficient disclosure to enable the invention to the full scope of the pending claims. The present specification clearly details the treatment of a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of the subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to the subject to treat the subject for at least one of the conditions as listed in Claim 1. For example, disclosure of conditions that may be treated using the subject methods can be found on p. 56, lines 3-11, and p. 57, line 10 to p. 59, line 11. Directions for treatment of the identified conditions by administering beta-blockers can be found, for example, on p. 14, line 14 to p. 25, line 4. Furthermore, the specification discloses methods of treating a condition such that the activities of the parasympathetic and sympathetic functions are substantially equal, for example, on p. 10, lines 11-15. Additionally, the specification discloses methods of determining that the parasympathetic and sympathetic functions are substantially equal, for example, on p. 48, lines 24-29.

Therefore, the Applicants assert that the methods disclosed in the present specification in conjunction with the knowledge available in the art at the time the

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1. *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2. *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8

present application was filed, would enable one of ordinary skill in the art to practice the invention to the full scope of the claims.

In re Wands Factors

In addition to the above, application of the *In re Wands* test to the facts of the present application leads to the conclusion that the presently pending claims are fully enabled, as demonstrated below.

In the present application, the Applicant maintains that the specification would enable one skilled in the art to use the invention without undue experimentation. In order to provide structure to the Applicant's response, each of the relevant enablement factors is further discussed in detail below.

The nature of the invention and the breadth of claims

The Examiner alleges that the claims are very broad, with respect to conditions, number of beta-blockers, and non-beta blocking agents (Office Action, p. 6)

However, the Applicants maintain that the present invention involves methods of treating conditions *that are caused by an autonomic nervous system abnormality*. In other words, the conditions all contain the common element of being caused by an autonomic nervous system abnormality, and therefore, are not as broad as the Examiner suggests. Furthermore, the conditions are treated by modulating the autonomic nervous system, with agents that are well-known in the art, i.e., beta-blockers, which are, as discussed above, adequately disclosed in the specification.

Claim 23 further contains the element of administering an effective amount of at least one non-beta-blocker, as disclosed on p. 34, line 9 to p. 47, line 20. Again, these are agents that are well-known in the art, and as such, the Applicants maintain that these non-beta blocker agents are adequately described in the specification.

Accordingly, the Applicants maintain that as discussed above, the conditions that may be treated, and the beta-blockers and non-beta blockers that may be administered

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USPQ2d 1400, 1404 (Fed. Cir. 1988).

are adequately disclosed, and therefore given the nature of the invention, the present application does enable a person skilled in the art to make and use the claimed invention.

The relative skill of those in the art

The Applicants agree with the Examiner's assertion that the skill level of an artisan, such as those in the pharmaceutical and medical arts, is high.

Predictability of the art

The Examiner states that despite the advanced training of those in the art, the art is highly unpredictable. The Examiner alleges that it is not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone, and that in order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered. (Office Action, p. 5-6)

As above, the Applicants respectfully disagree, and maintain that the underlying pathophysiology of the conditions being treated is clear. The claims of the present invention involve methods of treating conditions *that are caused by an autonomic nervous system abnormality*. In other words, the conditions all contain the common element of being caused by an autonomic nervous system abnormality. The method further includes treating the conditions that are caused by an autonomic nervous system abnormality with an effective amount of an agent (e.g., beta-blocker) which can affect the autonomic nervous system.

In making the rejection, the Examiner has cited Stockley ("Are Beta-Blockers Safe?" BMJ, 298, 10 Jun 1989) as evidence that "it is highly unpredictable what the outcome would be due to the interaction of beta blockers with other drugs" (Office Action, p. 7). Stockley was cited for disclosing that two patients developed cardiac failure upon administration of nifedipine with a beta-blocker.

However, the Applicants point out that Stockley also discloses that while "the combination of beta-blockers and nifedipine...sometimes causes problems", Stockley

also states that "concurrent use *can be valuable and usually uneventful*". In addition, Stockley states "*These [adverse] reports are few compared with those describing the advantages of concurrent use*" (p. 1584, paragraph 2, emphasis added) In other words, Stockley contains an anecdotal report of two patients with an adverse reaction, which can occur with any medication or treatment. In fact, in contrast to the Examiner's assertion, Stockley confirms that these drugs are commonly and successfully used together.

The Examiner has also cited Chester, et al. (Chest 79, 5, May 1981) for teaching adverse affects of propranolol on airway function in nonasthmatic chronic obstructive lung disease (COPD) patients, and therefore concludes that there is a high degree of unpredictability in a methods of the subject invention.

However, the Applicants again respectfully disagree, and assert that Chester concludes that "*propranolol does not usually cause a rapid and dramatic clinical exacerbation in most patients with nonasthmatic COPD*" (emphasis added), and "for patients with COPD who are receiving propranolol therapy for concurrent cardiovascular disease, we advise serial measurement of pulmonary function as a guide to detect possible deterioration" (p. 544, col. 1). And further, "[w]e could find no relation between the degree of response to propranolol and either the extent of baseline obstructive ventilatory dysfunction or the degree of improvement after isoproterenol. Since neither of these measurements can predict an adverse response to propranolol, each patient receiving propranolol must be observed for possible effect on their airways" (p. 542, col. 2).

In other words, Chester discloses what appears to be an adverse reaction in some patients that cannot be predicted, which as discussed above, can be a consequence of individual differences, and occur with any treatment or medication.

Accordingly, the Applicants assert that given the predictability of the prior art, and the disclosure in the specification, the present application does enable a person skilled in the art to make and use the claimed invention.

The state of the prior art

The Examiner again cites Stockley and Chester, and further cites Houston (Cardiol Clin, 1986, Feb 4(1), 117-135), Liebermann et al. (Br J Obstet Gynaecol, 1978, 678-83, abstract), Allen (citation not provided), and Salpeter et al (Cochrane Database of Systemic Reviews, 2, 2002) for support of the allegation that not every single disease will be effectively treated by beta-blockers, nor can every combination of beta-blocker with a non-beta-blocking agent be used without interactions and be effective in treatment (Office Action, p. 8)

However, the Applicants respectfully disagree, and point out that, as discussed above, both Stockley and Chester disclose reports of adverse reactions, which can occur with any medication or treatment. As discussed above, Stockley confirms that the combination of beta-blockers and calcium channel blockers *are* commonly and successfully used together. Chester teaches that in patients with COPD, there are no measurements that can predict an adverse response to propranolol, and therefore each patient receiving propranolol must be observed for possible effect on their airways. The Applicants maintain that these studies merely confirm the conclusion that, as with any treatment, patients must be monitored for side effects or adverse reactions.

Houston was cited for disclosing that beta-blockers without intrinsic sympathomimetic activity have an adverse affect on glucose tolerance. It appears from the abstract provided that this effect is primarily a problem in patients with diabetes or patients at risk for developing glucose intolerance. The Applicants point out, however, that the subject methods do not exclude treatment for other conditions, as an example, anti-diabetic agents are listed among the non-beta-blocker agents that may be used in the methods of the subject invention (see, for example, Claim 24). Additionally, the Applicants note that beta-blockers *with* intrinsic sympathomimetic activity are disclosed

in the specification and claims, for example, pindolol (p. 33, lines 10-11, and Claim 21) and acebutolol (p. 31, lines 17-18, and Claim 21)

Liebermann was cited for disclosing that beta-blockade is harmful to the hypoxic fetus. This study from 30 years ago involves a small number of patients (24) in which the outcomes were allegedly worse in patients treated with propranolol, however the abstract provided also states that *the probability of fetal or neonatal death was related to the amount of proteinuria and presence of renal parenchymal disease* (emphasis added). There is no disclosure of how these factors were controlled for, and there is no indication that there was a control population.

Salpeter was cited for teaching that "beta-blocker therapy has mortality benefits in patients with hypertension, heart failure, coronary artery disease as well as during the postoperative period" (Office Action, p. 8). The Applicants agree, and point out that Salpeter also discloses that "cardioselective beta-blockers given in mild to moderate reversible airway disease or COPD, [does] not produce adverse respiratory effects in the short term" (p. 2, lines 2-3).

The Applicants therefore maintain that given the state of the art, the claims are adequately enabled, as the references provided by the Examiner show that as with any treatment, adverse reactions and side effects are possible, and patients must be monitored carefully during treatment.

The amount of direction or guidance presented and the presence of working examples

In making the rejection, the Examiner has again stated that the specification does not provide support for administering a beta-blocker to treat a subject for at least one of the conditions in Claim 1, wherein modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

The Applicants respectfully disagree. The specification does provide extensive support for methods of administering beta-blockers to treat a subject, for example, on p. 14, line 14 to p. 25, line 4. Additionally, disclosure of conditions that may be treated

using the subject methods can be found, for example, on p. 56, lines 3-11, and p. 57, lines 10 to p. 59, line 11. There are specific examples disclosed in the specification, for example, as in the example of treatment of sudden infant death syndrome (SIDS), as disclosed on p. 59, lines 19-25, and p. 60, line 20 to p. 61, line 12. In this disclosure, the inventors have disclosed that a maladaptive shift to sympathetic bias may be a key determinant of SIDS, and additionally cited multiple references in support of this assertion. In the example of aging-associated conditions (as disclosed on p. 65, line 20 to p. 67, line 12), the inventors have determined that many conditions of aging are manifestations of sympathetic bias unmasked by withdrawal of parasympathetic function. Additional citations in support of the assertion can be found on p. 66, lines 13-27.

Furthermore, the specification also clearly describes the method wherein the activities of the parasympathetic and sympathetic functions are substantially equal, as for example, on p. 10, lines 11-15. The specification also clearly describes the method of determining that the parasympathetic and sympathetic functions are substantially equal, for example on p. 48, lines 24-29.

Accordingly, the Applicants maintain that the guidance provided in the specification, when taken in conjunction with the other enablement factors under *In re Wands*, provides the requisite amount of direction and guidance for a person skilled in the art to make and practice the invention to the full scope of the pending claims.

Furthermore, the Applicants respectfully note that under the *In re Wands* factors for determining compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph, the presence or absence or working examples is but a single factor to be taken in consideration with the other factors. As such, under *In re Wands*, the presence or absence of working examples is weighed against the other factors, such as the availability in the art of general guidelines relevant to the claimed invention and guidance provided in the specification.

Moreover, the Applicants cite *In re Robbins* and *In re Borkowski* to emphasize that compliance with the enablement requirement under Title 35 U.S.C. §112, first

paragraph does not require or mandate that a specific example be disclosed.[3] Accordingly, the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[4]

The Applicants assert that with the disclosure of the present application and that merely routine experimentation may be needed to practice the claimed method, no working example is required to make or use the claimed methods. Accordingly, the Applicant maintains that the present application does enable a person skilled in the art to make and use the claimed invention.

The quantity of experimentation needed

The Examiner states that "in order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary" (Office Action, p. 9). The Examiner alleges that it would require undue experimentation to test all beta-blockers for every single condition listed in Claim 1 and with combination of non-beta-blockers listed in Claim 24.

The Applicants again maintain that beta-blockers and the non-beta-blocker agents as specified in the claims are all well-known in the art. The inventive step is in the novel use of these well-known agents for treatment of conditions which have an underlying abnormality of the autonomic nervous system.

Accordingly, the Applicants assert that given the state of the prior art, and the disclosure in the specification, the present application does enable a person skilled in the art to make and use the claimed invention.

The Applicants note that the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP § 2164.01.[5] In *Hybritech*

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3 *In re Robins* 166 U.S.P.Q. 552 (CCPA 1970); *In re Borkowski,* 164 U.S.P.Q. 642 (CCPA 1970).
4. *In re Borkowski,* 164 USPQ at 642.
5. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

Inc. v. Monoclonal Antibodies, Inc., the Federal Circuit has held that where the "experiments are empirical in nature," as in the case of the present application, the court found that no undue experimentation is required.[6]

The Examiner states that "considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task" (Office Action, p. 10).

The Applicants respectfully disagree, arguing that the invention is directed to methods of treating a subject for a condition caused by an autonomic nervous system abnormality, comprising modulating at least a portion of the subject's autonomic nervous system with an effective amount of at least one beta-blocker. The method may further include administering an effective amount of at least one non-beta-blocker agent.

The inventive step, therefore, is a method of treating a subject for a condition caused by a previously undiscovered underlying cause, with a well-known agent (e.g., a beta-blocker), which for some of the conditions is a non-traditional agent, because the inventors have discovered that modulation of the autonomic nervous system can result in effective treatment for the condition. There is not, as the Examiner alleges, a requirement for testing each beta-blocker for all conditions listed, with every single non-beta blocker listed.

For example, many patients have a diagnosis of more than one condition (e.g, coronary artery disease, hypertension, renal insufficiency, diabetes, arthritis, etc.) As the Examiner has pointed out, adverse effects are possible with many medications, and as in the cited prior art above, in many cases it is not possible to predict which patients will have an adverse reaction to a particular drug. It is not necessary even for a new medication to be tested in every single person in order to determine if it is safe for patients, nor would it be practical for a physician to require "proof" that an exact combination of medications in a specific dose given to a particular patient will be *guaranteed* not to cause any adverse reactions before prescribing them for that patient. The Examiner seems to be suggesting that all possible combinations and side effects and adverse reactions be anticipated before a treatment is even considered. As the

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6 *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

Examiner has correctly stated, the level of one of ordinary skill in the pharmaceutical and medical arts is high, and the ability to choose an appropriate beta-blocker and in some embodiments an appropriate non-beta-blocker for treatment of a particular condition of a patient, e.g., treatment of a condition caused by an autonomic nervous system abnormality, with appropriate monitoring of potential side effects and adverse reactions is well within the level of skill of a physician, and is indeed, to be expected. The Applicants point out that it would be unusual to expect a physician to prescribe a drug, and then send a patient out with no follow-up.

Furthermore, the claims are directed to a method of treating a condition caused by an autonomic nervous system abnormality by directing therapy at the underlying cause, i.e, the autonomic nervous system abnormality. Beta-blockers are well known in the art, and the methods for assessing successful treatment, e.g., substantially equal parasympathetic and sympathetic functions, are described in the specification, for example, on p. 49, line 14 to p. 50, line 16, for example, and are also well known in the art. Therefore, the predictability in the art is high, and the quantity of experimentation low.

Accordingly, the Applicants maintain that the specification fully demonstrates the treatment of a condition caused by an autonomic nervous system abnormality by administering an effective amount of a beta-blocker. The Applicants maintain that the claims are enabled according to the pending claims without practicing undue experimentation.

For the reasons set forth above, the Applicants maintain that the enablement requirement to practice the method of treatment has been met because 1) the amount of experimentation required to practice the claimed methods would not be undue and excessive 2) guidance is given on how to practice such methods of treatment 3) it is not necessary to provide a working example, 4) the relative skill of those in the art is high, and 5) the breadth of claims is enabled by the specification. As such, one skilled in the art would be able to perform the experiments as a matter of routine. The specification,

therefore, provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Accordingly, the Applicants maintain that the current claims directed to methods of treating a subject for a condition caused by an autonomic nervous system abnormality by modulating at least a portion of the subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to treat for the condition, wherein modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal are sufficiently enabled by the specification.

In view of the foregoing discussion, the Applicants submit that the current claims are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of Claims 1, 3, 4, 11-28, 41, 62 and 63 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 3, 4, 14, 19-22, 28, 41, and 62 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see Akzo N.V. v. United States Int'l Trade Comm'n 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), cert denied, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art

reference must disclose every feature of the claimed invention, either explicitly or inherently. Glaxo v. Novopharm, Ltd. 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

In rejecting the present claims, the Examiner has noted that Gambardella does not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system, however, that since Gambardella teach the administration of propranolol 40 mg twice daily, that Gambardella inherently teaches that the modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system by administration of the same compound as claimed to the same set of patients with an abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application (Office Action, p. 12)

However, the Applicants maintain that as the claims as currently amended contain the element of determining that said parasympathetic and sympathetic functions are substantially equal, Gambardella does not anticipate the current claims, because Gambardella does not teach this element.

Gambardella fails to teach this element because the method in Gambardella discloses the use of propranolol in elderly weight-losing cancer patients to block the effects of the sympathetic nervous system. The goal of treatment disclosed in Gambardella is enhancement of daily caloric intake without increased energy expenditure (abstract).

Gambardella therefore fails to teach the element of treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic

nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

Accordingly, the Applicants maintain that Gambardella fails to anticipate the current claims, because Gambardella fails to teach each and every element of the rejected claims. Namely, Gambardella does not specifically disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein the method further comprises determining that said parasympathetic and sympathetic functions are substantially equal. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 14, 19-22, 28, 41, and 62 be withdrawn.

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, and 62 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Brevetti et al. (Brief communications, Nov. 1981, p 938-941).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

In making this rejection, the Examiner states that Brevetti does not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system, however, that since Brevetti teaches the administration of propranolol 40 mg three times daily, that the reference inherently teaches that the modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound as claimed to the same set of patients with an

abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application (Office Action, p. 13)

However, the Applicants maintain that as the claims as currently amended contain the element of determining that said parasympathetic and sympathetic functions are substantially equal, Brevetti does not anticipate the current claims, because Brevetti does not teach this element.

Brevetti was cited for disclosing treatment of an imbalance between the alpha- and beta-adrenoreceptor activity of the sympathetic nervous system (p. 941), however there is no discussion in Brevetti of the parasympathetic nervous system. Nowhere in Brevetti is there the element of modulating of the autonomic nervous system which results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system. Furthermore, Brevetti fails to teach the element of determining that the parasympathetic and sympathetic functions are substantially equal, as in the current claims.

Accordingly, the Applicants maintain that Brevetti fails to anticipate the current claims, because Brevetti fails to teach each and every element of the rejected claims. Namely, Brevetti does not specifically disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, and 62 be withdrawn.

Claims 1, 21, 23-25, and 28 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Davies, et al. (The J of Intl Med Research, 1988, 16, 173-181).

In making this rejection, the Examiner states that Davies does not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system, however, that since Davies teaches the administration of propranolol 40-240mg/day, that Davies inherently teaches that the modulation of the autonomic

nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound as claimed to the same set of patients with an abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application.(Office Action, p. 14)

However, the Applicants maintain that as the claims as currently amended contain the element of determining that said parasympathetic and sympathetic functions are substantially equal, Davies does not anticipate the current claims, because Davies does not teach this element.

Davies discloses that ibuprofen does not substantially affect treatment of hypertension in patients on beta-blockers or thiazides, however there is no discussion in Davies of the autonomic nervous system. Nowhere in Davies is there the element of modulating of the autonomic nervous system which results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and furthermore, there is no disclosure of determining that the parasympathetic and sympathetic functions are substantially equal.

Accordingly, the Applicants maintain that Davies fails to anticipate the current claims, because Davies fails to teach each and every element of the rejected claims. Namely, Davies does not specifically disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 21, 23-25, and 28 be withdrawn.

Claims 1 and 20 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Broder, et al. (U.S. Patent 6,284,800).

In making this rejection, the Examiner states that Broder does not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic

nervous system, however, that since Broder teaches the administration of propranolol 250mg/day, that Broder inherently teaches that the modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound as claimed to the same set of patients with an abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application (Office Action, p. 15)

However, the Applicants maintain that as the claims as currently amended contain the element of determining that said parasympathetic and sympathetic functions are substantially equal, Broder does not anticipate the current claims, because Broder does not teach this element. The Applicants also note that Broder discloses treatment with the "previously thought to be inactive" optical isomer D-propranolol, not the more commonly used L-propranolol.

Broder was cited for disclosing treatment of bronchorestriction in a human or animal, comprising administering an effective amount of a drug including D-propranolol. However, nowhere in Broder is there the element of modulating of the autonomic nervous system which results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system.

Broder therefore fails to teach the element of treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and furthermore, Broder fails to teach determining that the parasympathetic and sympathetic functions are substantially equal.

Accordingly, the Applicants maintain that Broder fails to anticipate the current claims, because Broder fails to teach each and every element of the rejected claims. Namely, Broder does not specifically disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 and 20 be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1 and 63 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003).

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007); Pharmastem Therapeutics v. Viacell et al., 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., KSR at 1741; Omegaflex, Inc. v. Parker-Hannifin Corp., 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing KSR. Further, the Supreme Court in KSR also stated that that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

In making this rejection, the Examiner states that Lampert does not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system, however, that since Lampert teaches the administration of propranolol 180 or 240 mg/day, that Lampert teaches that the modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same

compound as claimed to the same set of patients with an abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application.(Office Action, p. 16)

However, the Applicants maintain that as the claims as currently amended contain the element of determining that said parasympathetic and sympathetic functions are substantially equal, Lampert does not anticipate the current claims, because Lampert does not teach or suggest this element.

Lampert was cited for allegedly disclosing that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction. However, there is no disclosure in Lampert that teaches or suggests that the treatment will result in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and there is therefore no teaching or suggestion of determining that the parasympathetic and sympathetic functions are substantially equal.

Therefore, a prima facie case of obviousness has not been established because Lampert fails to teach or suggest all the elements of the rejected claims. Namely, Lampert does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 and 63 be withdrawn.

Claims 1, 16, and 18 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Guilli, et al. (Cardiovascular Research, 2001, 208-216) in view of Bugiardini, et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

In making this rejection, the Examiner states that Guilli teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (abstract). The Examiner notes that Guilli does not teach administration of a beta-blocker, however that Bugiardini et al teach administration of propranolol to patients with X syndrome. The Examiner then alleges that it would have been obvious to one of ordinary skill in the art to have administered a beta-blocker as disclosed in Bugiardini to a subject with an abnormally low parasympathetic activity as in Guilli.

The Examiner notes that the references do not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system, however, that since Bugiardini teaches the administration of propranolol 120 to 160 mg/day, that the reference teaches modulation of the autonomic nervous system that results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound as claimed to the same set of patients with an abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application.(Office Action, p. 17)

However, the Applicants maintain that as the claims as currently amended contain the element of determining that the parasympathetic and sympathetic functions are substantially equal, the combination of references does not render the claims obvious, because neither references teaches or suggests this element.

Guilli was cited for allegedly teaching that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity. However, as there is no disclosure in Guilli that teaches or suggests that the treatment will result in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, or any teaching or suggestion of determining that the parasympathetic and sympathetic functions are substantially equal, the addition of Bugiardini fails to make up for this deficiency.

Therefore, a prima facie case of obviousness has not been established because Guilli fails to teach or suggest all the elements of the rejected claims. Namely, Guilli does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at

least a portion of the autonomic nervous system, wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. The addition of Bugiardini fails to make up for this deficiency. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 16, and 18 be withdrawn.

Claims 1 and 26-27 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill, et al. (U.S. Patent 6,449,507) and Lampert, et al. (The Am J of Cardiology, 91, 2, Jan 2003).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

In making this rejection, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that administration of a beta blocker such as propranolol modulates or alters the sympathetic and parasympathetic activities of the autonomic nervous system as Hill teaches the stimulation of parasympathetic and sympathetic nerve fibers. The Examiner states that Hill does not explicitly teach that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system, however, that since Lampert teaches the administration of propranolol 180 or 240 mg/day, that Lampert teaches that the modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound as claimed to the same set of patients with an abnormality in the autonomic nervous system in a dosage recommended in the specification of the instant application.(Office Action, p. 19)

Lampert was cited for allegedly disclosing that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction. However,

the Applicants maintain that as the claims as currently amended contain the element of determining that the parasympathetic and sympathetic functions are substantially equal, and neither Hill nor Lampert teaches or suggests this element.

Therefore, a prima facie case of obviousness has not been established because Hill fails to teach or suggest all the elements of the rejected claims. Namely, Hill does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. The addition of Lampert fails to make up for this deficiency. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, and 26-27 be withdrawn.

Claims 1, 11, 13, and 24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Garrett, et al. (Quarterly J of Expt. Physiology, 1987, 72, 357-68).

An element of the rejected claims is modulating at least a portion of a subject's autonomic nervous system by administering an effective amount of at least one beta-blocker, wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, and wherein said method further comprises determining that said parasympathetic and sympathetic functions are substantially equal.

In making this rejection, the Examiner states that Garrett teaches the administration of a beta-blocker such as propranolol to modulate the autonomic nervous system in salivary glands. The Examiner alleges that by modulating the autonomic nervous system Garrett teaches the system with a high parasympathetic activity and a normal sympathetic activity (Office Action, p. 20)

However, the Examiner has not pointed to where the reference teaches or suggests that modulation of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Furthermore, nowhere in the reference is the teaching or suggestion of

determining that the parasympathetic and sympathetic functions are substantially equal, as in the current claims.

Therefore, a prima facie case of obviousness has not been established because Garrett fails to teach or suggest all the elements of the rejected claims. Namely, Garrett does not disclose treating a condition wherein modulating of the autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of the autonomic nervous system, wherein the method further comprises determining that the parasympathetic and sympathetic functions are substantially equal. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 11, 13, and 24 be withdrawn.

New Claims 64-68 are patentable over the art cited by the Examiner at least for the reasons cited above.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-002.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 12-4-2008 By: /Lynn Kidder, Reg. No. 56,107/
Lynn Kidder
Registration No. 56,107

Date: 12-4-2008 By: /Bret Field, Reg. No. 37,620/
Bret Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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